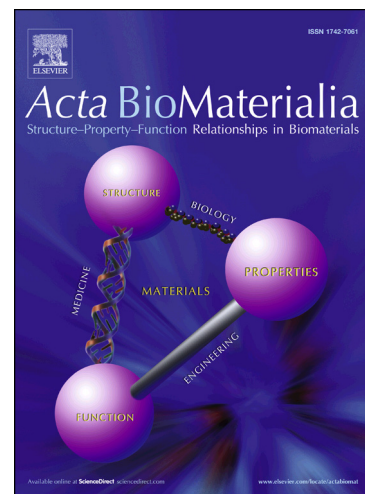# Accepted Manuscript

Review article

The blood compatibility challenge Part 3: Material associated activation of blood cascades and cells

Maud Gorbet, Claudia Sperling, Manfred F. Maitz, Christopher A. Siedleck, Carsten Werner, Michael V. Sefton

Please cite this article as: Gorbet, M., Sperling, C., Maitz, M.F., Siedleck, C.A., Werner, C., Sefton, M.V., The blood compatibility challenge Part 3: Material associated activation of blood cascades and cells, *Acta Biomaterialia* (2019), doi: https://doi.org/10.1016/j.actbio.2019.06.020

The blood compatibility challenge

Part 3: Material associated activation of blood cascades and cells

Maud Gorbet[1], Claudia Sperling[2], Manfred F. Maitz[2], Christopher A. Siedleck[3], Carsten Werner[2], Michael V. Sefton[4]

[1] Department of System Design Engineering, University of Waterloo, Waterloo, Ontario, Canada
[2] Institute Biofunctional Polymer Materials, Max Bergmann Center of Biomaterials, Leibniz-Institut für Polymerforschung Dresden e.V., Dresden, Germany
[3] Departments of Surgery and Bioengineering, The Pennsylvania State University, College of Medicine, Hershey, PA 17033, United States
[4] Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada

Abstract

Following protein adsorption/activation which is the first step after the contact of material surfaces and whole blood (part 2), fibrinogen is converted to fibrin and platelets become activated and assembled in the form of a thrombus. This thrombus formation is the key feature that needs to be minimized in the creation of materials with low thrombogenicity. Further aspects of blood compatibility that are important on their own are complement and leukocyte activation which are also important drivers of thrombus formation. Hence this chapter summarizes the state of knowledge on all of these cascades and cells and their interactions. For each cascade or cell type, the chapter distinguishes that which is in widespread agreement from what there is less of a consensus.

Statement of significance

This paper is part 3 of a series of 4 reviews discussing the problem of biomaterial associated thrombogenicity. The objective was to highlight features of broad agreement and provide commentary on those aspects of the problem that were subject to dispute. We hope that future investigators will update these reviews as new scholarship resolves the uncertainties of today.

Introduction

Biomaterials at once activate several defense systems of the body, Figure 1. The humoral systems of coagulation and complement strongly interact with platelets and immune cells and recently yet

more interactions between thrombogenic and immunologic processes have been discovered. We discuss those systems separately and then refer to the manifold interactions at the relevant sections.

Coagulation Cascade

Biomaterials drive the generation of thrombin and the conversion of fibrinogen to fibrin necessitating the administration of heparin or other anticoagulants. The cascade of clotting factors beginning with Factor XII are amongst those in the protein adsorbate [1]. Activation of the coagulation pathway also activates the kinin-kallikrein system (via FXIIa), complement (via Factor XIIa, kallikrein, thrombin) and platelets (via thrombin). When endothelium is damaged, for example via biomaterial implantation, thrombomodulin levels decrease and tissue factor increases creating another source of thrombin [2] and the potential for activation of the intrinsic pathway via thrombin-mediated activation of FXI.

Follow on comments:

In the absence of biomaterials, tissue factor is regarded as the key driver of coagulation following vascular injury. Biomaterial associated coagulation on the other hand can be related to the surface activity of contact phase molecules, which have a relatively strong abundance in the protein adsorbate, suggesting a prominent role for contact activation. Also polyphosphate nanoparticles on activated blood platelets were reported to activate coagulation via Factor XII [3]. However, it is interesting to note that under physiological conditions, the absence of Factor XII or other contact proteins (HMWK, kallikrein) has not been associated with abnormal bleeding [4]. Overall, evidence seems to suggest that FXII activation by biomaterial contact activates the intrinsic coagulation cascade, leading to formation of a clot. Yet there are other pathways that may augment or even replace the contact activation proteins in inducing biomaterial-induced coagulation.

The surface of activated blood platelets accelerate the coagulation cascade to produce thrombin, providing an amplification path that also links platelet and protein-mediated thrombosis [5].

There are multiple links between inflammatory and coagulant pathways. The role of blood born tissue factor in leukocytes and perhaps blood platelets [6, 7] in thrombosis and blood clot propagation has been highlighted [8, 9], and consequently some have argued that leukocyte activation and tissue factor release (and the extrinsic pathway) are key drivers also for biomaterial induced coagulation in blood [10-13]. On the other hand, the relevance of blood-born tissue factor for initiation of the coagulation (in distinction to propagation) is not generally accepted. A correlation between leukocyte inflammatory response and tissue factor expression has been demonstrated *in vitro* [11]. While the contribution of tissue factor (TF) involvement in the initiation of clotting in an ovine hemodialysis-model was shown [13], a correlation between leukocyte activation and blood clotting could not be demonstrated under defined *in vitro* conditions [11]. The rapid inactivation of tissue factor in blood has been regarded as the reason for this.

The impact of neutrophil elastase and cathepsin G on clot formation has also recently been further demonstrated in mice and highlights the complexity of the interactions taking place in clot formation and growth [14, 15].

Factor VII activating protease (FSAP or hyaluronic acid binding protein 2: HABP2) is a serine protease, supporting the extrinsic pathway of clotting activation by interfering with tissue factor

pathway inhibitor and by direct FVII activation. FSAP is activated by positively charged macromolecules [16] and surfaces [17] and may present an additional pathway of biomaterial induced coagulation activation.

Reliable analysis of blood coagulation has to reflect the complexity of the different activation pathways. Clotting times using whole blood or plasma using one of the established methods are crude measures of the ability of a material to activate the coagulation cascade. Whether plasma or whole blood is used to assess the properties of a test material further is a critical parameter. The pure initiation of the coagulation cascade does not necessarily lead to thrombus formation, but, as indicated above, the propagation from coagulation to the clot requires the presence of activated platelets [5].

Thrombin as a parameter of blood clotting is difficult to measure directly, because it is inactivated within seconds to the thrombin-antithrombin (TAT) complex, especially in presence of heparin. Prothrombin F1+2 fragment as byproduct of thrombin formation, the TAT-complex or fibrinopeptide A as byproduct of fibrin activation present more useful integral parameters of coagulation activation. More sophisticated measures such as thrombin generation rate may be more useful since one can incorporate such measures in mathematical models that may enable predictions under a wider range of experimental and perhaps even real-world conditions. A critical thrombin generation rate constant was one such parameter that was defined [18].

Ultimately though, all materials will drive plasma to coagulate following material contact unless anticoagulants are used. These levels of coagulation may not be clinically significant in many applications, but under *in vitro* conditions, placing blood in contact with a synthetic material will ultimately result in formation of a clot [19]. The lack of clinically significant levels of coagulation may arise from the dilutional effects of blood flow or from the continued presence of natural anticoagulants.

The need to use anticoagulants during blood collection argues against the above noted key role of tissue factor, although it is possible that clot initiation happens prior to the blood hitting the test tube. In that case though, one could not produce a blood sample that would not clot, effectively muting the ability to even study the problem anywhere other than in a person implanted with a material, and post-surgical recovery.

Hemolysis can influence thrombosis [20-22] through an effect on coagulation and other processes, although this is not well studied in the context of biomaterials. It has been thought that hemolysis is a consequence of shear stress in a device such as in a left ventricular assist device and not an effect of the material per se.

Platelet Activation

Platelet activation through biomaterials occurs via adhesion to adsorbed proteins (mainly fibrinogen) and indirectly through biomaterials-induced activation of coagulation and other systems. Platelet activation leads to spreading, a change in shape [23] and adhesion to surfaces as well as to platelets or to other cells via the GPIIb/IIIa receptor and P-selectin. It boosts the coagulation cascade by expression of phosphatidylserine, leads to the formation of microparticles, thromboxane formation and release of granule content [5, 24, 25]. These activated platelets create a nidus for thrombin generation and ultimately, occlusive thrombus formation or embolization. Such activation by biomaterials has been noted in experimental animals in several clinical scenarios [26-28]. In other situations, platelet activation is a useful diagnostic of potentially adverse interactions [27, 29].

Follow on comments

Material surface properties will affect the exposure of platelet binding regions in adsorbed proteins, and therefore affect the adhesion/activation of platelets. There are good correlations between the exposure of the γ-chain dodecapeptide in fibrinogen and platelet adhesion [30-32].

Platelet activation can occur with but also without adhesion to a material surface [26, 27]. Frequently, the activation level of adherent blood platelets is used as a measure of thrombogenicity and scored according to the platelet morphology. Small non-spreading cells are regarded as least activated while a pancake-like appearance show the highest activation level with several levels of pseudopod formation as intermediate stages [23, 33]. However, the platelet density on a surface and their morphology do not always correlate with thrombogenicity: various hydrogels are not thrombo-adhesive, but they support platelet aggregation and embolization. Furthermore, highly spreading blood platelets on hydrophobic materials are found which show clinically low thrombogenicity. A passivating effect of these blood platelets is assumed [34-36].

Activated platelets upregulate surface receptors like GPIIb/IIIa and P-selectin (CD62P), which is an important marker of platelet activation *in vivo*. The tendency of activated platelets to form platelet-leukocyte aggregates and stick to surfaces may suppress the level of detected P-selectin expression and raise the need for alternative parameters [37]. Release products of platelets, such as PF4 or β-TG release are established parameters [38, 39]. The platelet-leukocyte aggregates as such correlate with thrombotic events with cardiovascular devices and are suggested as a marker of platelet activation [40]. Material-induced aggregate formation has not been consistently characterized *in vivo*, making it difficult to correlate results from *in vitro* studies as well as testing the validity of the *in vitro* models used.

Platelet adhesion and activation are shear dependent processes. The platelet itself is shear sensitive [41, 42] and von Willebrand factor (vWF), the ligand for the platelet adhesion receptor GPIb, undergoes shear dependent exposure of the adhesion motifs [43]. Therefore, the response of platelets in arterial and venous settings may be different and hemocompatibility tests need to consider and report the shear conditions. Levels and types of shear stress highly differ depending

on the device and thus improvement in *in vitro* blood compatibility due to changes in material chemistry may have little clinical impact, because the influence of flow predominates [44]. As an extreme case, modern continuous flow LVADs can lead to bleeding by destruction of the high molecular weight vWF multimers that are critical for platelet adhesion in capillaries [45].

Activated platelets release $0.1 - 1$ µm sized microparticles (MPs) budding off from the cell membrane. Several animal and clinical studies have demonstrated that these MPs contribute to a pro-thrombotic state through the expression of phosphatidylserine and TF. This is true not just for platelets MPs but also for endothelial cells, monocytes and neutrophils MPs [46]. Cardiovascular materials have demonstrated to induce MP formation with significant impact on thrombosis and inflammation in animal experiments as well as clinical studies, highlighting the need of the biomaterial community to assess these as a form of material-induced activation and a biocompatibility marker. The presence of microparticles generated by LVAD in patients is also believed to contribute to endothelial dysfunction inducing a prothrombotic and pro-inflammatory state in patients, which can also alter the ability of endothelial cells to release vasodilatory mediators [47, 48]. The direct link between MPs and adverse events (such as stroke, organ failure, myocardial infarction), however, remains difficult to identify due to the limited number of clinical studies and the small number of patients involved.

Sefton believes that complement activation (particularly at the level of C1) is important for both adhesion and activation of blood platelets [49]. Recent research shows that C1q binds to platelets and is activated, leading to further complement activation through an increase in C3a [50-52]. The binding of C1q occurs either through a specific C1q receptor or through P-selectin after platelet activation. Complement activation may occur earlier than platelet activation, although it is likely that there is substantive crosstalk precluding such delineation. Given the crosstalk among these systems, platelet and leukocyte activation also occur in an interdependent fashion, albeit to different extents at different times.

In vitro platelet analysis in the frame of hemocompatibility assessment has several limitations. It is difficult to determine when platelet activation by a biomaterial, observed in *in vitro* assays, becomes clinically relevant; the same is generally true for any hemocompatibility parameter. Consequently, use of the term "highly activating" is of limited value without quantitative definition. Despite evidence that platelet functions and reactivity from patients with cardiovascular disease differ from healthy individuals [53-55], pre-clinical *in vitro* studies continue to be performed with the blood of healthy donors. This estimation of hemocompatibility therefore does not necessarily reflect the clinical performance and more tests with blood from patients should be performed.

Complement

The complement system, made up from more than 30 proteins is evolutionary related to the blood coagulation cascade and contributes to host defense. Biomaterials activation of the complement cascade leads to the release of reactive fragments C3a, C5a and SC5b-9 to plasma while complement proteins including C1q and C3b are often found in the protein adsorbate [56, 57]. The alternative pathway is particularly relevant for surfaces bearing a nucleophile group (OH, NH$_2$) capable of covalent binding of C3b [58, 59]. Complement inhibitors such as Factor H or C1q inhibitor may also bind to biomaterial surfaces or be incorporated into the protein adsorbate, such that complement activation is downregulated [60].

Follow on comments:

Different pathways may be involved in biomaterials induced complement activation [61]. Surface induced activation of the alternative pathway was reported to be a consequence of nucleophilic surface groups – but several reports propose that this effect is conferred via adsorbed proteins and not via the chemical moiety itself [62, 63]. Some suggest [59] that mostly hydroxylic groups are responsible for strong complement activation and activation through amino groups seems to be less relevant. The classical pathway may be activated by C1q binding to non-specifically adsorbed immunoglobins (IgG, IgM) on a foreign surface as well as to non-self patterns on surfaces and gets activated to initiate the complement cascade [64]. Only few reports propose a mannose pathway involvement through adsorbed, glycosylated proteins [65] or nanoparticles [66].

Besides the activation of the complement cascade, biomaterials may affect also the course of the cascade. Complement inhibitors (Factor H, C1q inhibitor) interacting with surfaces crucially modulate the resulting complement activation [57]. Surface topography on a nanoscale range, like the high surface curvature of nanoparticles can sterically prevent the interaction of adsorbed complement factors and thus block the propagation of the complement cascade [67].

Activation of the complement system mainly has inflammatory consequences. Complement fragment C5a is a strong activator of myeloid leukocytes via their complement receptor C5aR1 (CD88). The adhesion of these cells to a complement-activating surface is mainly triggered by the presence of surface-bound complement fragment C3b [58].

Complement activation induced by the biomaterial at the site of implantation may also lead to deposition of complement products on endothelial cells and production of endothelial microparticles which can contribute to the pro-inflammatory and thrombotic state [68]. C1q has also been shown to modulate endothelial cells behavior and to play a role in angiogenesis [69]. While these processes have been studied *in vitro* and in thrombotic diseases, they have been poorly characterized with cardiovascular devices [68].

The complement system also has several links to the coagulation system, both of which proceed in parallel in the protein adsorbate: coagulation factor XIIa can activate complement component C1 and thrombin can function as a C5 convertase [70]. In addition, the fibrinolytic plasmin has activity as a C5 convertase [71]. The complement system can modify coagulation by activating leukocytes to express and activate blood-born tissue factor [11, 70, 72, 73] or plasminogen

activator inhibitor (PAI-1) [74]. As mentioned above, activated platelets can support complement activation by binding complement fragments to P-selectin and the C1q receptor [49, 75].

Heparin acts as inhibitor in both systems by association with either antithrombin (coagulation) or factor H (complement).

Complement activation *in vitro* is typically measured in serum, since calcium and magnesium are required cofactors (precluding the use of citrate or EDTA) and heparin is an inhibitor of some reactions but not all, complicating result interpretation. If whole blood or blood plasma has to be used, then hirudin can be used as anticoagulant, as it does not interact with the complement system [76]. The soluble fragment complement C5a is a possible analyte for the common, terminal complement pathway. Fast binding of C5a to its receptor on granulocytes may quench the concentration of the free peptide [77] and quantification of the soluble terminal complement complex (sC5b-9) has been suggested as a more reliable parameter to determine the activation of the complement cascade [78]. If differentiation between the classical or alternative pathway is desired, then quantification of Bb (alternative pathway) and C4d (classical pathway) or the use of specific inhibitors can help, however in advanced stages usually the whole complement cascade is activated.

The critical threshold for complement related incompatibility is undefined, yet it is presumed that higher amounts indicate greater incompatibility. While 5 mg/mL SC5b-9 is readily detectable, it is unclear whether this level (~ 1/3 of positive controls such as zymosan) is biologically significant.

Leukocyte Activation

Like platelets, myeloid leukocytes (neutrophils and monocytes) may adhere or be activated on a surface. Their adhesion to biomaterials is mediated via different factors with adsorbed proteins (fibrinogen, fibronectin and iC3b) being of primary importance. Upregulation of CD11b, loss of L-selectin, release of reactive oxygen species (oxidative burst), neutrophil elastase, cathepsin G or IL-8 are typical markers of activation [79, 80]. These release products lead to local tissue damage and recruitment and activation of more inflammatory cells.

Follow-on comments

Triggers for leukocyte activation on materials mainly are adsorbed proteins and adherent platelets. Additionally, mechanical factors and contamination with endotoxins may induce leukocyte activation.

Adsorbed and soluble complement products are the most prominent triggers of granulocyte and monocyte activation. Above all the anaphylatoxic peptides C3a and C5a induce cell activation [12] while adherence to the surface is mediated through surface-bound iC3b that binds to CD11b/CD18 [81]. Other pathways, such as kallikrein-induced activation, also contribute to the activation [82] and adherence can occur to already adsorbed and activated platelets [83, 84]. Little is known about how eosinophils react to bare materials, yet there is evidence that they may become activated with drug-coated materials (such as stents) [85, 86].

Physical factors of biomedical devices, such as disturbed flow in LVAD and cardiopulmonary bypass (CPB), also present a source of leukocyte activation and contribute to a pro-thrombotic and pro-inflammatory state of leukocytes [80].

An additional "external" factor that may also affect leukocyte activation are lipopolysaccharides (LPS) from Gram negative bacteria, which are also commonly known as endotoxin. They can easily contaminate the surface of cardiovascular devices and biomaterials synthesized in the lab [87]. A contaminated surface can activate several components of the inflammatory and thrombotic response in blood. Therefore all materials should be tested for endotoxin contamination prior to *in vitro* and *in vivo* studies [88, 89].

The first innate inflammatory response against foreign materials in blood includes neutrophils and monocytes. When activated, internal cell reorganization will lead to the presentation of CD11b and other adhesion ligands on the cell surface. This enables the cells to adhere to the surface and to interact with other neutrophils, monocytes and platelets. Additionally, they release soluble factors (elastase, myeloperoxidase) and microparticle and can form neutrophil extracellular traps (NETs).

Similarly to platelet microparticles, leukocyte microparticles play a role in hemostasis and inflammation and contribute to pathological conditions [90]. No *in vitro* study has yet characterized the mechanisms associated with material-induced leukocyte microparticles. There is however clinical evidence that leukocyte microparticles generated with cardiovascular devices such as CPB and LVAD also contribute to endothelial dysfunction and coagulation [47, 48].

Granulocyte activation also can lead to NETosis (neutrophil extracellular trap formation), which is characterized by the expulsion of nuclear DNA along with citrullinated histones and granular content (e.g. elastase) [91]. These components are highly thrombogenic [92] and have been identified in thrombi from coronary arteries [93] and from failed stents [86]. While these have become an area of active research in thrombosis and inflammation [94, 95], the biomaterials community has been slow to recognize the potential impact of NETs in biocompatibility and limited *in vitro* studies exist. Recently, Sperling and Maitz suggested that NETs may also contribute to biomaterial-induced thrombogenicity [96]. The formation of NETs was also observed on CoCr (a common biomaterial used in stents) in the presence of platelets in vitro [97].

It is generally considered that biomaterials do not induce an adaptive, lymphocyte dependent immune response [98] but this may deserve more attention in hemocompatibility research [99]. There are a few cases, like nickel or chromium allergy, where released ions transform self-proteins to foreign epitopes and induce a T-cell response. It is startling that in the absence of an antigen, T cells can be activated, but it was reported that cytokines at the inflammatory site around the implant may cause a non-clonal bystander activation of T-cells [100]. A recent paper [101] points to a pivotal role for B cells in the foreign body response.

The activation of immune responses sometimes also has distinct beneficial effects. Microbial infection is a persistent risk for implant materials in the body and antimicrobial defense is a leading task of neutrophil granulocytes. The antimicrobial capacity of biomaterials-adherent neutrophils however is still largely unexplored [102], which significantly affects our ability to design cardiovascular biomaterials that can resist infection. Whole blood incubation was shown to support anti-microbial activity against various gram-positive and gram-negative strains [103]. On the other hand, other studies indicate that neutrophils have been shown to promote bacterial growth and to create a protective environment for biofilms [104, 105].

More positive effects of material-induced inflammation were noted for endothelial regeneration following vascular prosthetic implants [106]. Activated neutrophils can support monocyte infiltration and subsequent phenotype switching may suggest a beneficial impact [107]. Since biomaterial implantation, inter alia, damages blood vessels, transmigration through activated endothelium may not be the primary mechanism for generating of monocyte-derived tissue macrophages. In addition, there are tissue resident macrophages that are different from the monocyte-derived phenotype [108]. Conversely, the inflammatory response in the surrounding tissue induced by cardiovascular implantation may also result in the release of macrophage wound healing factors that could promote endothelialization.

In the context of an inflammatory response, the variety of cytokines generated will dictate the consequences of that response. Pro-inflammatory properties (M1) of macrophages activated by Interferon γ and pro-regenerative properties (M2) after activation by IL4 or IL10, for example, are observed [109] *in vitro*. The relevance of these clear M1/M2 distinctions *in vivo* is less clear, , although the notion of phenotypic differences among macrophages has been exploited in recent *in vivo* biomaterial studies [110, 111]. It has also been suggested that neutrophils can exhibit distinct phenotypes and may thus play different roles in inflammation, all the more so in the presence of biomaterials [112-114]; but this concept is not yet widely accepted.

Leukocyte activation manifests itself in diverse forms, and the mechanisms of crosstalk between platelets and leukocytes have been well demonstrated, blurring the line between inflammation and thrombosis [84]. Activated leukocytes can directly contribute to plasma coagulation on various pathways. They express tissue factor and contribute to coagulation in the process of thrombosis [12, 115-117]. The relevance of this pathway in biomaterial-associated thrombogenicity, however is unclear [11].

In addition to local effects of cell adhesion / activation systemic clinical consequences that have been directly related to leukocyte activation include infection, myocardial infarction as well as organ injury and failure [80, 118]. Leukocyte removal filters have been introduced in cardiopulmonary bypass (CPB) [119] yet released inflammatory mediators from the trapped cells could contribute to the inflammatory response [120].

In an *in vitro* model, the determination of leukocyte activation is limited to local effects. Additionally, usually blood donation is done by healthy donors while clinical complications may result from the altered state of leukocytes in ill patients. Leukocytes are generally in a state of higher activation in cardiovascular diseases, such as in heart failure and left ventricular dysfunction [121, 122]. This can further contribute to complications following implantation of a medical device. Preclinical hemocompatibility testing will need to address these clinical conditions better in the future.

References

[1] Y. Wu, Contact pathway of coagulation and inflammation, Thrombosis Journal 13 (2015) 17.

[2] V.W.M. van Hinsbergh, Endothelium—role in regulation of coagulation and inflammation, Seminars in Immunopathology 34(1) (2012) 93-106.

[3] J.J.F. Verhoef, A.D. Barendrecht, K.F. Nickel, K. Dijkxhoorn, E. Kenne, L. Labberton, O.J.T. McCarty, R. Schiffelers, H.F. Heijnen, A.P. Hendrickx, H. Schellekens, M.H. Fens, S. de Maat, T. Renné, C. Maas, Polyphosphate nanoparticles on the platelet surface trigger contact system activation, Blood 129(12) (2017) 1707.

[4] T. Renné, A.H. Schmaier, K.F. Nickel, M. Blombäck, C. Maas, In vivo roles of factor XII, Blood 120(22) (2012) 4296-4303.

[5] C. Sperling, M. Fischer, M.F. Maitz, C. Werner, Blood coagulation on biomaterials requires the combination of distinct activation processes, Biomaterials 30(27) (2009) 4447-56.

[6] N.S. Key, Platelet tissue factor: how did it get there and is it important?, Seminars in Hematology 45(2 Suppl 1) (2008) S16-20.

[7] M. Brambilla, L. Facchinetti, P. Canzano, L. Rossetti, N. Ferri, A. Balduini, V. Abbonante, D. Boselli, L. De Marco, M.N. Di Minno, V. Toschi, A. Corsini, E. Tremoli, M. Camera, Human megakaryocytes confer tissue factor to a subset of shed platelets to stimulate thrombin generation, Thrombosis and Haemostasis 114(3) (2015) 579-92.

[8] J.F. Vojacek, Should We Replace the Terms Intrinsic and Extrinsic Coagulation Pathways With Tissue Factor Pathway?, Clinical and Applied Thrombosis/Hemostasis 23(8) (2017) 922-927.

[9] N. Mackman, R.E. Tilley, N.S. Key, Role of the Extrinsic Pathway of Blood Coagulation in Hemostasis and Thrombosis, Arteriosclerosis, Thrombosis, and Vascular Biology 27(8) (2007) 1687-1693.

[10] M.B. Gorbet, M.V. Sefton, Material-induced tissue factor expression but not CD11b upregulation depends on the presence of platelets, Journal of Biomedical Materials Research Part A 67(3) (2003) 792-800.

[11] M. Fischer, C. Sperling, P. Tengvall, C. Werner, The ability of surface characteristics of materials to trigger leukocyte tissue factor expression, Biomaterials 31 (2010) 2498-507.

[12] I. Kourtzelis, M.M. Markiewski, M. Doumas, S. Rafail, K. Kambas, I. Mitroulis, S. Panagoutsos, P. Passadakis, V. Vargemezis, P. Magotti, H. Qu, T.E. Mollnes, K. Ritis, J.D. Lambris, Complement anaphylatoxin C5a contributes to hemodialysis-associated thrombosis, Blood 116(4) (2010) 631-9.

[13] S. Lakbakbi, A. Debrumetz, C. Terryn, J. Szymezak, P. Rieu, P. Nguyen, Tissue factor expressed by adherent cells contributes to hemodialysis-membrane thrombogenicity, Thrombosis Research 144 (2016) 218-223.

[14] R. Darbousset, C. Delierneux, S. Mezouar, A. Hego, C. Lecut, I. Guillaumat, M.A. Riederer, R.J. Evans, F. Dignat-George, L. Panicot-Dubois, C. Oury, C. Dubois, P2X1 expressed on polymorphonuclear neutrophils and platelets is required for thrombosis in mice, Blood 124(16) (2014) 2575-85.

[15] D.S. Woulfe, PMNs deliver first aid to clot, Blood 124(16) (2014) 2475-6.

[16] S. Yamamichi, M. Nishitani, N. Nishimura, Y. Matsushita, K. Hasumi, Polyamine-promoted autoactivation of plasma hyaluronan-binding protein, Journal of Thrombosis and Haemostasis 8(3) (2010) 559-66.

[17] C. Sperling, M.F. Maitz, S. Grasso, C. Werner, S.M. Kanse, A Positively Charged Surface Triggers Coagulation Activation Through Factor VII Activating Protease (FSAP), ACS Applied Materials & Interfaces 9(46) (2017) 40107-40116.

[18] G. Rollason, M.V. Sefton, Measurement of the rate of thrombin production in human plasma in contact with different materials, Journal of Biomedical Materials Research 26 (1992) 675-693.

[19] E.A. Vogler, C.A. Siedlecki, Contact activation of blood-plasma coagulation, Biomaterials 30(10) (2009) 1857-69.

[20] C. L'Acqua, E. Hod, New perspectives on the thrombotic complications of haemolysis, British Journal of Haematology 168(2) (2015) 175-85.

[21] J.W. Weisel, R.I. Litvinov, Red blood cells: the forgotten player in hemostasis and thrombosis, Journal of Thrombosis and Haemostasis 17(2) (2019) 271-282.

[22] C.R. Bartoli, D. Zhang, J. Kang, S. Hennessy-Strahs, D. Restle, J. Howard, G. Redline, C. Bermudez, P. Atluri, M.A. Acker, Clinical and In Vitro Evidence That Subclinical Hemolysis Contributes to LVAD Thrombosis, The Annals of Thoracic Surgery 105(3) (2018) 807-814.

[23] S.L. Goodman, T.G. Grasel, S.L. Cooper, R.M. Albrecht, Platelet shape change and cytoskeletal reorganization on polyurethaneureas, Journal of Biomedical Materials Research 23(1) (1989) 105-23.

[24] L. Totani, V. Evangelista, Platelet-leukocyte interactions in cardiovascular disease and beyond, Arteriosclerosis, Thrombosis, and Vascular Biology 30(12) (2010) 2357-61.

[25] S.L. Diamond, Systems Analysis of Thrombus Formation, Circulation Research 118(9) (2016) 1348-1362.

[26] C.H. Cholakis, W. Zingg, M.V. Sefton, Effect of heparin-PVA hydrogel on platelets in a chronic canine arterio-venous shunt, Journal of Biomedical Materials Research 23(4) (1989) 417-41.

[27] S.R. Hanson, L.A. Harker, B.D. Ratner, A.S. Hoffman, In vivo evaluation of artificial surfaces with a nonhuman primate model of arterial thrombosis, Journal of Laboratory and Clinical Medicine 95(2) (1980) 289-304.

[28] M. Finsterbusch, W.C. Schrottmaier, J.B. Kral-Pointner, M. Salzmann, A. Assinger, Measuring and interpreting platelet-leukocyte aggregates, Platelets (2018) 1-9.

[29] M.V. Sefton, A. Sawyer, M. Gorbet, J.P. Black, E. Cheng, C. Gemmel, E. Pottinger-Cooper, Does surface chemistry affect thrombogenicity of surface modified polymers?, Journal of Biomedical Materials Research 55 (2001) 447-459.

[30] W.-B. Tsai, J.M. Grunkemeier, T.A. Horbett, Variations in the ability of adsorbed fibrinogen to mediate platelet adhesion to polystyrene-based materials: A multivariate statistical analysis of antibody binding to the platelet binding sites of fibrinogen, Journal of Biomedical Materials Research Part A 67A(4) (2003) 1255-1268.

[31] V. Balasubramanian, N.K. Grusin, R.W. Bucher, V.T. Turitto, S.M. Slack, Residence-time dependent changes in fibrinogen adsorbed to polymeric biomaterials, Journal of Biomedical Materials Research 44(3) (1999) 253-260.

[32] P. Soman, Z. Rice, C.A. Siedlecki, Measuring the Time-Dependent Functional Activity of Adsorbed Fibrinogen by Atomic Force Microscopy, Langmuir 24(16) (2008) 8801-8806.

[33] R.D. Allen, L.R. Zacharski, S.T. Widirstky, R. Rosenstein, L.M. Zaitlin, D.R. Burgess, Transformation and motility of human platelets: details of the shape change and release reaction observed by optical and electron microscopy, Journal of Cell Biology 83(1) (1979) 126-42.

[34] M.V. Sefton, C.H. Gemmell, M.B. Gorbet, Nonthrombogenic treatments and strategies, in: B.D. Ratner, A.S. Hoffman, F.J. Schoen, J.E. Lemons (Eds.), Biomaterials Science. An introduction to materials in medicine, Academic Press2012.

[35] C.L. Haycox, B.D. Ratner, In vitro platelet interactions in whole human blood exposed to biomaterial surfaces: insights on blood compatibility, Journal of Biomedical Materials Research 27(9) (1993) 1181-93.

[36] L.M. Szott, C.A. Irvin, M. Trollsas, S. Hossainy, B.D. Ratner, Blood compatibility assessment of polymers used in drug eluting stent coatings, Biointerphases 11(2) (2016) 029806.

[37] A.D. Michelson, M.R. Barnard, L.A. Krueger, C.R. Valeri, M.I. Furman, Circulating monocyte-platelet aggregates are a more sensitive marker of in vivo platelet activation than platelet surface P-selectin: studies in baboons, human coronary intervention, and human acute myocardial infarction, Circulation 104(13) (2001) 1533-7.

[38] N. Weber, H.P. Wendel, G. Ziemer, Hemocompatibility of heparin-coated surfaces and the role of selective plasma protein adsorption, Biomaterials 23(2) (2002) 429-39.

[39] C. Sperling, M.F. Maitz, C. Werner, Test methods for hemocompatibility of biomaterials, in: C.A. Siedlecki (Ed.), Hemocompatibility of biomaterials for clinical applications. Blood-biomaterials interactions, Woodhead, Duxford, Cambridge, Kidlington, 2017, pp. 77-104.

[40] C. Cerletti, C. Tamburrelli, B. Izzi, F. Gianfagna, G. de Gaetano, Platelet-leukocyte interactions in thrombosis, Thrombosis Research 129(3) (2012) 263-266.

[41] J. Ding, Z. Chen, S. Niu, J. Zhang, N.K. Mondal, B.P. Griffith, Z.J. Wu, Quantification of Shear-Induced Platelet Activation: High Shear Stresses for Short Exposure Time, Artificial Organs 39(7) (2015) 576-83.

[42] W.S. Nesbitt, E. Westein, F.J. Tovar-Lopez, E. Tolouei, A. Mitchell, J. Fu, J. Carberry, A. Fouras, S.P. Jackson, A shear gradient-dependent platelet aggregation mechanism drives thrombus formation, Nature Medicine 15(6) (2009) 665-673.

[43] S.W. Schneider, S. Nuschele, A. Wixforth, C. Gorzelanny, A. Alexander-Katz, R.R. Netz, M.F. Schneider, Shear-induced unfolding triggers adhesion of von Willebrand factor fibers, Proceedings of the National Academy of Sciences of the United States of America 104(19) (2007) 7899-903.

[44] H.T. Spijker, R. Graaff, P.W. Boonstra, H.J. Busscher, W. van Oeveren, On the influence of flow conditions and wettability on blood material interactions, Biomaterials 24(26) (2003) 4717-4727.

[45] A. Nascimbene, S. Neelamegham, O.H. Frazier, J.L. Moake, J.-F. Dong, Acquired von Willebrand syndrome associated with left ventricular assist device, Blood 127(25) (2016) 3133-41.

[46] A.P. Owens, 3rd, N. Mackman, Microparticles in hemostasis and thrombosis, Circulation Research 108(10) (2011) 1284-97.

[47] R. Sansone, B. Stanske, S. Keymel, D. Schuler, P. Horn, D. Saeed, U. Boeken, R. Westenfeld, A. Lichtenberg, M. Kelm, C. Heiss, Macrovascular and microvascular function after implantation of left ventricular assist devices in end-stage heart failure: Role of microparticles, J Heart Lung Transplant 34(7) (2015) 921-32.

[48] A. Nascimbene, R. Hernandez, J.K. George, A. Parker, A.L. Bergeron, S. Pradhan, K.V. Vijayan, A. Civitello, L. Simpson, M. Nawrot, V.V. Lee, H.R. Mallidi, R.M. Delgado, J.F. Dong, O.H. Frazier, Association between cell-derived microparticles and adverse events in patients with nonpulsatile left ventricular assist devices, J Heart Lung Transplant 33(5) (2014) 470-7.

[49] E.I. Peerschke, W. Yin, B. Ghebrehiwet, Platelet mediated complement activation, Advances in Experimental Medicine and Biology 632 (2008) 81-91.

[50] E.I. Peerschke, W. Yin, S.E. Grigg, B. Ghebrehiwet, Blood platelets activate the classical pathway of human complement, Journal of Thrombosis and Haemostasis 4(9) (2006) 2035-42.

[51] O.A. Hamad, K.N. Ekdahl, P.H. Nilsson, J. Andersson, P. Magotti, J.D. Lambris, B. Nilsson, Complement activation triggered by chondroitin sulfate released by thrombin receptor-activated platelets, Journal of Thrombosis and Haemostasis 6(8) (2008) 1413-21.

[52] E.I. Peerschke, W. Yin, B. Ghebrehiwet, Complement activation on platelets: implications for vascular inflammation and thrombosis, Molecular Immunology 47(13) (2010) 2170-5.

[53] S. Braune, M. Gross, M. Walter, S. Zhou, S. Dietze, S. Rutschow, A. Lendlein, C. Tschope, F. Jung, Adhesion and activation of platelets from subjects with coronary artery disease and apparently healthy individuals on biomaterials, Journal of Biomedical Materials Research Part B: Applied Biomaterials 104(1) (2016) 210-7.

[54] G. Patti, C. Proscia, G. Di Sciascio, Antiplatelet therapy in patients with diabetes mellitus and acute coronary syndrome, Circulation journal : official journal of the Japanese Circulation Society 78(1) (2014) 33-41.

[55] A.I. Vinik, T. Erbas, T.S. Park, R. Nolan, G.L. Pittenger, Platelet dysfunction in type 2 diabetes, Diabetes Care 24(8) (2001) 1476-85.

[56] P. Tengvall, A. Askendal, Ellipsometric in vitro studies on blood plasma and serum adsorption to zirconium, Journal of Biomedical Materials Research 57(2) (2001) 285-90.

[57] A.E. Engberg, J.P. Rosengren-Holmberg, H. Chen, B. Nilsson, J.D. Lambris, I.A. Nicholls, K.N. Ekdahl, Blood protein-polymer adsorption: Implications for understanding complement-mediated hemoincompatibility, Journal of Biomedical Materials Research Part A 97A(1) (2011) 74-84.

[58] C. Sperling, M.F. Maitz, S. Talkenberger, M.F. Gouzy, T. Groth, C. Werner, *In vitro* blood reactivity to hydroxylated and non-hydroxylated polymer surfaces, Biomaterials 28(25) (2007) 3617-25.

[59] M. Toda, T. Kitazawa, I. Hirata, Y. Hirano, H. Iwata, Complement activation on surfaces carrying amino groups, Biomaterials 29(4) (2008) 407-17.

[60] M.P. Carreno, D. Labarre, F. Maillet, M. Jozefowicz, M.D. Kazatchkine, Regulation of the human alternative complement pathway: formation of a ternary complex between factor H, surface-bound C3b and chemical groups on nonactivating surfaces, European Journal of Immunology 19(11) (1989) 2145-50.

[61] K.N. Ekdahl, J.D. Lambris, H. Elwing, D. Ricklin, P.H. Nilsson, Y. Teramura, I.A. Nicholls, B. Nilsson, Innate immunity activation on biomaterial surfaces: A mechanistic model and coping strategies, Advanced drug delivery reviews 63(12) (2011) 1042-1050.

[62] J. Andersson, K.N. Ekdahl, J.D. Lambris, B. Nilsson, Binding of C3 fragments on top of adsorbed plasma proteins during complement activation on a model biomaterial surface, Biomaterials 26(13) (2005) 1477-1485.

[63] F. Chen, G. Wang, J.I. Griffin, B. Brenneman, N.K. Banda, V.M. Holers, D.S. Backos, L. Wu, S.M. Moghimi, D. Simberg, Complement proteins bind to nanoparticle protein corona and undergo dynamic exchange in vivo, Nat Nanotechnol 12(4) (2017) 387-393.

[64] Y.-H. Kang, L.A. Tan, M.V. Carroll, M.E. Gentle, R.B. Sim, Target pattern recognition by complement proteins of the classical and alternative pathways, Advances in Experimental Medicine and Biology 653 (2009) 117-28.

[65] E. Hein, P. Garred, The lectin pathway of complement and biocompatibility, Advances in Experimental Medicine and Biology 865 (2015) 77-92.

[66] S.M. Moghimi, P. Wibroe Peter, L. Wu, Z.S. Farhangrazi, Insidious pathogen-mimicking properties of nanoparticles in triggering the lectin pathway of the complement system, European Journal of Nanomedicine, 2015, p. 263.

[67] M. Hulander, A. Lundgren, M. Berglin, M. Ohrlander, J. Lausmaa, H. Elwing, Immune complement activation is attenuated by surface nanotopography, Int J Nanomedicine 6 (2011) 2653-66.

[68] D. Karpman, A.L. Stahl, I. Arvidsson, K. Johansson, S. Loos, R. Tati, Z. Bekassy, A.C. Kristoffersson, M. Mossberg, R. Kahn, Complement Interactions with Blood Cells, Endothelial Cells and Microvesicles in Thrombotic and Inflammatory Conditions, Advances in Experimental Medicine and Biology 865 (2015) 19-42.

[69] F. Bossi, C. Tripodo, L. Rizzi, R. Bulla, C. Agostinis, C. Guarnotta, C. Munaut, G. Baldassarre, G. Papa, S. Zorzet, B. Ghebrehiwet, G.S. Ling, M. Botto, F. Tedesco, C1q as a unique player in angiogenesis with
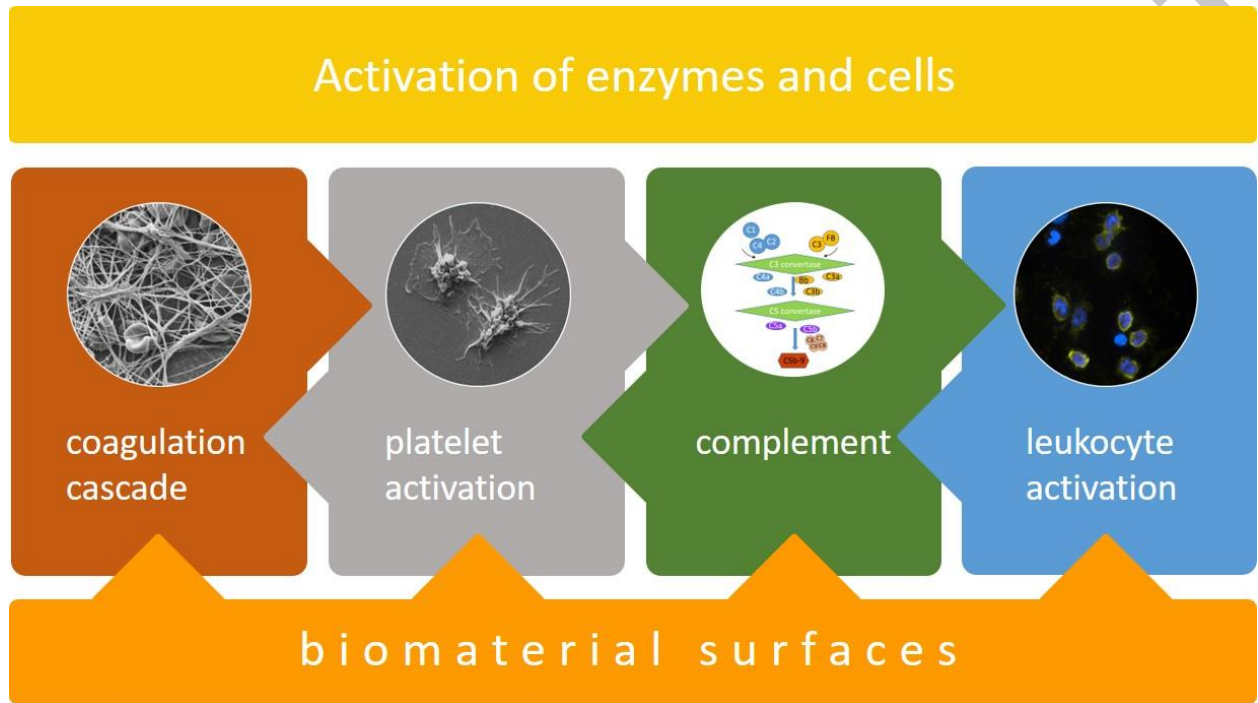
therapeutic implication in wound healing, Proceedings of the National Academy of Sciences of the United States of America 111(11) (2014) 4209-14.

[70] D. Rittirsch, M.A. Flierl, P.A. Ward, Harmful molecular mechanisms in sepsis, Nature reviews. Immunology 8(10) (2008) 776-787.

[71] J.H. Foley, B.L. Walton, M.M. Aleman, A.M. O'Byrne, V. Lei, M. Harrasser, K.A. Foley, A.S. Wolberg, E.M. Conway, Complement Activation in Arterial and Venous Thrombosis is Mediated by Plasmin, EBioMedicine 5 (2016) 175-82.

[72] J.H. Foley, E.M. Conway, Cross talk pathways between coagulation and inflammation, Circulation Research 118(9) (2016) 1392-1408.

[73] S. Subramaniam, K. Jurk, L. Hobohm, S. Jackel, M. Saffarzadeh, K. Schwierczek, P. Wenzel, F. Langer, C. Reinhardt, W. Ruf, Distinct contributions of complement factors to platelet activation and fibrin formation in venous thrombus development, Blood 129(16) (2017) 2291-2302.

[74] S.P. Kastl, W.S. Speidl, C. Kaun, G. Rega, A. Assadian, T.W. Weiss, P. Valent, G.W. Hagmueller, G. Maurer, K. Huber, J. Wojta, The complement component C5a induces the expression of plasminogen activator inhibitor-1 in human macrophages via NF-κB activation, Journal of Thrombosis and Haemostasis 4(8) (2006) 1790-7.

[75] I. Del Conde, M.A. Cruz, H. Zhang, J.A. Lopez, V. Afshar-Kharghan, Platelet activation leads to activation and propagation of the complement system, Journal of Experimental Medicine 201(6) (2005) 871-9.

[76] F. Bexborn, A.E. Engberg, K. Sandholm, T.E. Mollnes, J. Hong, K.N. Ekdahl, Hirudin versus heparin for use in whole blood *in vitro* biocompatibility models, Journal of Biomedical Materials Research Part A 89A(4) (2009) 951-959.

[77] T.E. Mollnes, T.S. Jokiranta, L. Truedsson, B. Nilsson, S. Rodriguez de Cordoba, M. Kirschfink, Complement analysis in the 21st century, Molecular Immunology 44(16) (2007) 3838-49.

[78] M. Berger, B. Broxup, M.V. Sefton, Using ELISA to evaluate complement activation by reference biomaterials, Journal of Materials Science: Materials in Medicine 5 (1994) 622-627.

[79] M.B. Gorbet, M.V. Sefton, Biomaterial-associated thrombosis: roles of coagulation factors, complement, platelets and leukocytes, Biomaterials 25(26) (2004) 5681-5703.

[80] L. Grosman-Rimon, F. Billia, A. Fuks, I. Jacobs, A.M. M, D.Z. Cherney, V. Rao, New therapy, new challenges: The effects of long-term continuous flow left ventricular assist device on inflammation, Int J Cardiol 215 (2016) 424-30.

[81] B. Nilsson, K.N. Ekdahl, T.E. Mollnes, J.D. Lambris, The role of complement in biomaterial-induced inflammation, Molecular Immunology 44(1-3) (2007) 82-94.

[82] Y.T. Wachtfogel, U. Kucich, H.L. James, C.F. Scott, M. Schapira, M. Zimmerman, A.B. Cohen, R.W. Colman, Human plasma kallikrein releases neutrophil elastase during blood coagulation, Journal of Clinical Investigation 72(5) (1983) 1672-1677.

[83] A.E. Asberg, V. Videm, Activation of neutrophil granulocytes in an in vitro model of a cardiopulmonary bypass, Artificial Organs 29(12) (2005) 927-936.

[84] M. Ghasemzadeh, E. Hosseini, Platelet-leukocyte crosstalk: Linking proinflammatory responses to procoagulant state, Thrombosis Research 131(3) (2013) 191-197.

[85] G. Niccoli, D. Schiavino, F. Belloni, G. Ferrante, G. La Torre, M. Conte, N. Cosentino, R.A. Montone, V. Sabato, F. Burzotta, C. Trani, A.M. Leone, I. Porto, M. Pieroni, G. Patriarca, F. Crea, Pre-intervention eosinophil cationic protein serum levels predict clinical outcomes following implantation of drug-eluting stents, Eur Heart J 30(11) (2009) 1340-7.

[86] J. Riegger, R.A. Byrne, M. Joner, S. Chandraratne, A.H. Gershlick, J.M. Ten Berg, T. Adriaenssens, G. Guagliumi, T.C. Godschalk, F.J. Neumann, D. Trenk, L.J. Feldman, P.G. Steg, W. Desmet, F. Alfonso, A.H. Goodall, R. Wojdyla, D. Dudek, V. Philippi, S. Opinaldo, A. Titova, N. Malik, J. Cotton, D.A. Jhagroe, A.A. Heestermans, P. Sinnaeve, P. Vermeersch, C. Valina, C. Schulz, A. Kastrati, S. Massberg, I. Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort, Histopathological evaluation of thrombus in patients presenting with stent thrombosis. A multicenter European study: a report of the
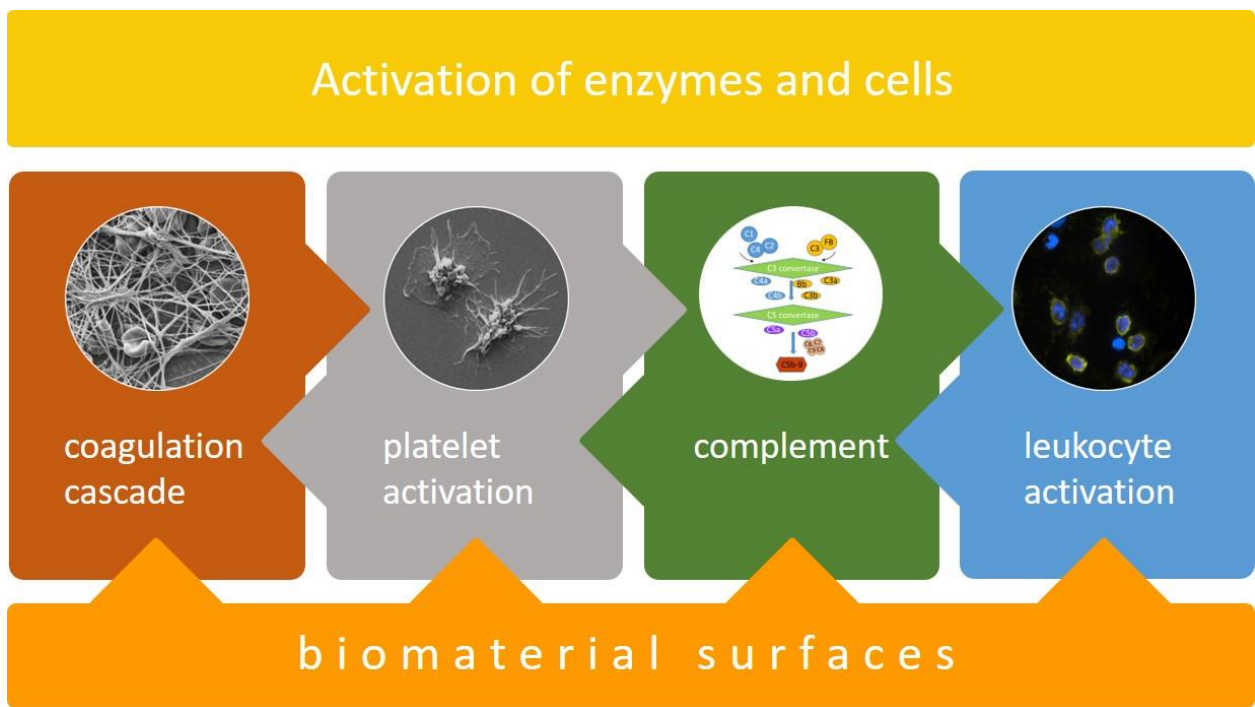
prevention of late stent thrombosis by an interdisciplinary global European effort consortium, Eur Heart J 37(19) (2016) 1538-49.

[87] M.B. Gorbet, M.V. Sefton, Complement inhibition reduces material-induced leukocyte activation with PEG modified polystyrene beads (Tentagel) but not polystyrene beads, Journal of Biomedical Materials Research Part A 74(4) (2005) 511-522.

[88] K. Stang, S. Krajewski, B. Neumann, J. Kurz, M. Post, S. Stoppelkamp, S. Fennrich, M. Avci-Adali, D. Armbruster, C. Schlensak, I.A. Burgener, H.P. Wendel, T. Walker, Hemocompatibility testing according to ISO 10993-4: discrimination between pyrogen- and device-induced hemostatic activation, Mater Sci Eng C Mater Biol Appl 42 (2014) 422-8.

[89] M.B. Gorbet, M.V. Sefton, Endotoxin: the uninvited guest, Biomaterials 26(34) (2005) 6811-7.

[90] A. Angelillo-Scherrer, Leukocyte-derived microparticles in vascular homeostasis, Circulation Research 110(2) (2012) 356-69.

[91] V. Brinkmann, U. Reichard, C. Goosmann, B. Fauler, Y. Uhlemann, D.S. Weiss, Y. Weinrauch, A. Zychlinsky, Neutrophil extracellular traps kill bacteria, Science 303(5663) (2004) 1532-5.

[92] T.J. Gould, T.T. Vu, L.L. Swystun, D.J. Dwivedi, S.H.C. Mai, J.I. Weitz, P.C. Liaw, Neutrophil extracellular traps promote thrombin generation through platelet-dependent and platelet-independent mechanisms, Arteriosclerosis, Thrombosis, and Vascular Biology 34(9) (2014) 1977-1984.

[93] D.A. Stakos, K. Kambas, T. Konstantinidis, I. Mitroulis, E. Apostolidou, S. Arelaki, V. Tsironidou, A. Giatromanolaki, P. Skendros, S. Konstantinides, K. Ritis, Expression of functional tissue factor by neutrophil extracellular traps in culprit artery of acute myocardial infarction, Eur Heart J 36(22) (2015) 1405-14.

[94] V. Delgado-Rizo, M. Martínez-Guzmán, L. Iñiguez-Gutierrez, A. García-Orozco, A. Alvarado-Navarro, M. Fafutis-Morris, Neutrophil extracellular traps and its implications in inflammation: an overview, Frontiers in Immunology 8(81) (2017).

[95] K. Martinod, D.D. Wagner, Thrombosis: tangled up in NETs, Blood 123(18) (2014) 2768-76.

[96] C. Sperling, M. Fischer, M.F. Maitz, C. Werner, Neutrophil extracellular trap formation upon exposure of hydrophobic materials to human whole blood causes thrombogenic reactions, Biomaterials Science 5(10) (2017) 1998-2008.

[97] V. Ollivier, C. Roques, N. Receveur, M. Gratz, L. Feldman, D. Letourneur, C. Gachet, P.H. Mangin, M. Jandrot-Perrus, Bioreactivity of stent material: Activation of platelets, coagulation, leukocytes and endothelial cell dysfunction in vitro, Platelets 28(6) (2017) 529-539.

[98] A. Rodriguez, J.M. Anderson, Evaluation of Clinical Biomaterial Surface Effects on T Lymphocyte Activation, Journal of biomedical materials research. Part A 92(1) (2010) 214-220.

[99] J.M. Anderson, A.K. McNally, Biocompatibility of implants: lymphocyte/macrophage interactions, Seminars in immunopathology 33(3) (2011) 221-33.

[100] S. Landgraeber, M. von Knoch, F. Löer, A. Wegner, M. Tsokos, B. Hußmann, M. Totsch, Extrinsic and intrinsic pathways of apoptosis in aseptic loosening after total hip replacement, Biomaterials 29(24-25) (2008) 3444-3450.

[101] J.C. Doloff, O. Veiseh, A.J. Vegas, H.H. Tam, S. Farah, M. Ma, J. Li, A. Bader, A. Chiu, A. Sadraei, S. Aresta-Dasilva, M. Griffin, S. Jhunjhunwala, M. Webber, S. Siebert, K. Tang, M. Chen, E. Langan, N. Dholokia, R. Thakrar, M. Qi, J. Oberholzer, D.L. Greiner, R. Langer, D.G. Anderson, Colony stimulating factor-1 receptor is a central component of the foreign body response to biomaterial implants in rodents and non-human primates, Nature Materials 16(6) (2017) 671-680.

[102] F. Gunther, G.H. Wabnitz, P. Stroh, B. Prior, U. Obst, Y. Samstag, C. Wagner, G.M. Hansch, Host defence against Staphylococcus aureus biofilms infection: phagocytosis of biofilms by polymorphonuclear neutrophils (PMN), Molecular Immunology 46(8-9) (2009) 1805-13.

[103] S. Schulz, M. Maitz, S. Hänsel, L.D. Renner, C. Werner, Analyzing the antiseptic capacity of silver-functionalized poly(ethylene glycol)-heparin hydrogels after human whole blood exposure, Biomaterials Science, 2018.

[104] Q.M. Parks, R.L. Young, K.R. Poch, K.C. Malcolm, M.L. Vasil, J.A. Nick, Neutrophil enhancement of Pseudomonas aeruginosa biofilm development: human F-actin and DNA as targets for therapy, J Med Microbiol 58(Pt 4) (2009) 492-502.

[105] P.O. Jensen, M. Kolpen, K.N. Kragh, M. Kuhl, Microenvironmental characteristics and physiology of biofilms in chronic infections of CF patients are strongly affected by the host immune response, APMIS 125(4) (2017) 276-288.

[106] F. Boccafoschi, C. Mosca, M. Ramella, I. Carmagnola, V. Chiono, G. Ciardelli, M. Cannas, Biological evaluation of materials for cardiovascular application: the role of the short-term inflammatory response in endothelial regeneration, Journal of Biomedical Materials Research Part A 101(11) (2013) 3131-40.

[107] M. Horckmans, L. Ring, J. Duchene, D. Santovito, M.J. Schloss, M. Drechsler, C. Weber, O. Soehnlein, S. Steffens, Neutrophils orchestrate post-myocardial infarction healing by polarizing macrophages towards a reparative phenotype, Eur Heart J 38(3) (2017) 187-197.

[108] C.S. Robbins, I. Hilgendorf, G.F. Weber, I. Theurl, Y. Iwamoto, J.L. Figueiredo, R. Gorbatov, G.K. Sukhova, L.M. Gerhardt, D. Smyth, C.C. Zavitz, E.A. Shikatani, M. Parsons, N. van Rooijen, H.Y. Lin, M. Husain, P. Libby, M. Nahrendorf, R. Weissleder, F.K. Swirski, Local proliferation dominates lesional macrophage accumulation in atherosclerosis, Nat Med 19(9) (2013) 1166-72.

[109] D.M. Mosser, J.P. Edwards, Exploring the full spectrum of macrophage activation, Nature reviews. Immunology 8(12) (2008) 958-69.

[110] I. Talior-Volodarsky, R. Mahou, D. Zhang, M. Sefton, The role of insulin growth factor-1 on the vascular regenerative effect of MAA coated disks and macrophage-endothelial cell crosstalk, Biomaterials 144 (2017) 199-210.

[111] D. Hachim, S.T. LoPresti, C.C. Yates, B.N. Brown, Shifts in macrophage phenotype at the biomaterial interface via IL-4 eluting coatings are associated with improved implant integration, Biomaterials 112 (2017) 95-107.

[112] G.S. Selders, A.E. Fetz, M.Z. Radic, G.L. Bowlin, An overview of the role of neutrophils in innate immunity, inflammation and host-biomaterial integration, Regen Biomater 4(1) (2017) 55-68.

[113] C. Silvestre-Roig, A. Hidalgo, O. Soehnlein, Neutrophil heterogeneity: implications for homeostasis and pathogenesis, Blood 127(18) (2016) 2173-2181.

[114] A. Mantovani, M.A. Cassatella, C. Costantini, S. Jaillon, Neutrophils in the activation and regulation of innate and adaptive immunity, Nature reviews. Immunology 11(8) (2011) 519-31.

[115] L.L. Swystun, P.C. Liaw, The role of leukocytes in thrombosis, Blood 128(6) (2016) 753-762.

[116] N. Maugeri, A.A. Manfredi, Tissue Factor Expressed by Neutrophils: Another Piece in the Vascular Inflammation Puzzle, Seminars in Thrombosis and Hemostasis 41(7) (2015) 728-36.

[117] E. Shantsila, G.Y. Lip, The role of monocytes in thrombotic disorders. Insights from tissue factor, monocyte-platelet aggregates and novel mechanisms, Thrombosis and Haemostasis 102(5) (2009) 916-24.

[118] C.S. Rinder, M. Fontes, J.P. Mathew, H.M. Rinder, B.R. Smith, G. Multicenter Study of Perioperative Ischemia Research, Neutrophil CD11b upregulation during cardiopulmonary bypass is associated with postoperative renal injury, The Annals of Thoracic Surgery 75(3) (2003) 899-905.

[119] S. Boodram, E. Evans, Use of leukocyte-depleting filters during cardiac surgery with cardiopulmonary bypass: a review, J Extra Corpor Technol 40(1) (2008) 27-42.

[120] F. Bakhtiary, A. Moritz, P. Kleine, O. Dzemali, A. Simon, H. Ackermann, S. Martens, Leukocyte depletion during cardiac surgery with extracorporeal circulation in high risk patients, Inflammation Research 57(12) (2008) 577-585.

[121] N.K. Mondal, E.N. Sorensen, S.M. Pham, S.C. Koenig, B.P. Griffith, M.S. Slaughter, Z.J. Wu, Systemic Inflammatory Response Syndrome in End-Stage Heart Failure Patients Following Continuous-Flow Left Ventricular Assist Device Implantation: Differences in Plasma Redox Status and Leukocyte Activation, Artificial Organs 40(5) (2016) 434-43.

[122] V. Rudolph, T.K. Rudolph, J.C. Hennings, S. Blankenberg, R. Schnabel, D. Steven, M. Haddad, K. Knittel, S. Wende, J. Wenzel, T. Munzel, T. Heitzer, T. Meinertz, C. Hubner, S. Baldus, Activation of

polymorphonuclear neutrophils in patients with impaired left ventricular function, Free Radic Biol Med 43(8) (2007) 1189-96.